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CASE PRESENTATION

Neonatal hemophagocytic syndrome. Case report

Síndrome hemofagocítico neonatal. Reporte de caso

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ABSTRACT

Introduction: hemophagocytic syndrome or hemophagocytic lymphohistiocytosis is characterized by a pathological activation of the immune system mediated by cytotoxic T lymphocytes, natural killers and macrophages, which finally phagocytize hematopoietic cells.
Case presentation: term newborn, appropriate weight for gestational age, son of a multiparous mother, habitual aborter, with a personal pathological history of joint hypermobility and chronic gastritis. He was born in good condition and in his evolution presented respiratory distress, exanthema, fever, pancytopenia, marked hepatomegaly and elevated serum ferritin with clinical-analytical worsening and rapid progression to multiple organ dysfunction, with negative virological studies and no bacterial or fungal growth. Hemophagocytic syndrome was diagnosed and specific treatment was prescribed: dexamethasone and immunoglobulin at immunosuppressive doses. The neonate had a torpid evolution and died at 27 days of life.
Conclusions: hemophagocytic syndrome in the neonatal period is difficult to diagnose and behaves as a simulator of many diseases with rapid progression to multiorgan failure and very unfavorable prognostic implications for the patient.

Keywords: Infant, Newborn; Tissues; Lymphohistiocytosis, Hemophagocytic.

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RESUMEN

Introducción: el síndrome hemofagocítico o linfohistiocitosis hemofagocítica se caracteriza por una activación patológica del sistema inmune mediada por linfocitos T citotóxicos, natural killers y macrófagos, que finalmente fagocitan las células hematopoyéticas.
Presentación de caso: recién nacido a término, peso adecuado para la edad gestacional, hijo de madre multípara, abortadora habitual, con antecedentes patológicos personales de hipermovilidad articular y gastritis crónica. Nació en buenas condiciones y en su evolución presentó distrés respiratorio, exantema, fiebre, pancitopenia, hepatomegalia marcada y ferritina sérica elevada con empeoramiento clínico-analítico y rápida progresión a la disfunción múltiple de órganos, con estudios virológicos negativos y sin crecimiento bacteriano ni micótico. Se diagnosticó síndrome hemofagocítico con prescripción de tratamiento específico: dexametasona e inmunoglobulina a dosis inmunosupresora. El neonato tuvo una evolución tórpida y fallece con 27 días de vida.
Conclusiones: el síndrome hemofagocítico en el período neonatal es difícil de diagnosticar y se comporta como un simulador de muchas enfermedades con rápida progresión al fallo multiorgánico e implicaciones pronósticas muy desfavorables para el paciente.

Palabras clave: Recién Nacido; Tejidos; Síndrome Hemofagocítico.

INTRODUCTION

Hemophagocytic syndrome (HPS) or hemophagocytic lymphohistiocytosis is characterized by a pathologic activation of the immune system mediated by cytotoxic T lymphocytes, natural killers and macrophages, which ultimately phagocytize hematopoietic cells. It was described in 1952 as a disorder of immunity. Its origin is associated with familial inheritance (primary form) as well as infections, oncologic, rheumatologic and metabolic diseases (secondary form). In both types of presentation a deficiency in cytotoxicity has been demonstrated which leads to abnormal T-lymphocyte activation and cytokine production.[1,2,3]

The result is an excessive and persistent activation of antigen presenting cells (histiocytes and macrophages) and T lymphocytes (CD8) which produces a massive increase in the proliferation of these cells and ectopic migration of T cells, with phenomena of hemophagocytosis. The terminology SHF is based on the presence of phagocytic macrophages of the three hematological.[4]

It is important to identify its existence early, since it is a life-threatening entity due to its rapid capacity to generate multiorgan involvement. The establishment of effective treatment at an early stage can lead to a better prognosis for the patient.[5]

There are few epidemiological studies on the disease, however, the worldwide incidence is estimated to be 1.2 cases per million inhabitants, although this figure may be underestimated due to the difficulty in making the diagnosis because the symptoms and signs of the disease are not very specific.[1,6]

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CASE PRESENTATION

Male newborn, son of a 29-year-old mother with a personal pathological history of joint hypermobility and chronic gastritis, obstetric history of four pregnancies and three spontaneous abortions, non-reactive VDRL serology and negative HIV. Product of a euthyroid delivery, at 40,4 weeks gestational age, with a membrane rupture time of four hours, fluid meconium amniotic fluid, Apgar 9-9 points and a birth weight of 3580 grams.

At 9 hours of life he was transferred to the neonatal intensive care unit for presenting tachypnea (72 breaths per minute) and intercostal retractions with a diagnosis of respiratory distress syndrome due to meconium aspiration of amniotic fluid for which specific treatment was initiated. On admission, the decubitus chest X-ray showed no acute pleuropulmonary lesions and laboratory studies were within physiological limits. The enteral route was suspended and parenteral feeding was started due to the presence of porraceous gastric contents.

At four days of extrauterine life, with no signs of respiratory distress, she presented fever of 38,5 degrees Celsius, hypoactivity, abdominal distension, hepatomegaly, jaundice and refusal of food. An infectious origin was suspected, and complementary evolutionary tests were indicated where metabolic acidosis and mild thrombocytopenia were found (Tables 1 and 2), so antimicrobial coverage was extended with meronen and gentamicin according to microbiological map.

Treatment with vasoactive drugs (dopamine and dobutamine) was added due to hemodynamic disorders at 10 days of life, despite having negative blood cultures and acute phase reactants. He also required mechanical ventilation, invasive modality and evolved by complementary. Exanthematous manifestations appeared and the icterus intensified. According to clinical and analytical evolution, hematocrit figures were negative.

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He presented easy bleeding from the puncture sites and macroscopic hematuria despite the continuous use of blood products. Antimicrobial therapy was escalated. Alterations in the peripheral lamina persisted (hypochromia with anisocytosis, leukopenia, severe neutropenia and thrombocytopenia) and the diagnostic possibility of a hemophagocytic syndrome was suspected due to the torpid evolution of the patient without response to the indicated treatment, the absence of bacterial and fungal growth, with virological studies also negative.

Medulogram was performed for diagnostic progression. The marrow smear was scarce, without the possibility of evaluating the integrity of the systems or the myelo-erythroid ratio, isolated cells of the granulopoietic system were observed in all stages of maturation without evidence of the megakaryopoietic system. The existence of histiocytes phagocytizing cells of the erythroid and granulopoietic systems was determined without leukemic infiltration or presence of cells foreign to the medullary parenchyma.

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Table 1. Main results of laboratory studies. General Teaching Hospital "Abel Santamaría Cuadrado". Pinar del Río.

Studies	**Results according to postnatal age**			
	At birth	**4 days**	**10 days**	**15 days**
	0,64 L/L	0,54 L/L	0,30 L/L	0,23 L/L
Blood gases capillary	pH: 7,38 PCO2 :40 mm Hg PO2:48 mm Hg HCO3: 22,3 meq/L BE: 2,2 meq/L	pH: 7,32 PCO2: 45 mm Hg PO2: 46 mm Hg HCO3: 18 meq/L BE : 5 meq/L	pH: 7,20 PCO2: 68 mm Hg PO2: 41 mm Hg HCO3: 16 meq/L BE: 7 meq/L	pH: 7.28 PCO2: 47 mm Hg PO2: 51 mm Hg HCO3: 17 meq/L BE : 9 meq/L
Liver and lipid profile BI		BI: 13 mg/dl	TGP:27 UI TGO:49 UI BD: 3,8 mg/dl	TGP: 32 IU TGO: 13 IU GGT: 126 IU FA: 237 IU Albumin: 26 g/L Prot. tot: 42 g/L BD: 5,1 mg/dl LDH: 388 IU Triglycerides: 1,15 mmol/L Cholesterol: 2,3 mmol/L
Coagulogram:	Platelets: (200x109/L) T. Prothrombin Control: 13 sec Patient: 14sec T. P. Thromboplast. Control: 35 sec Patient: 30 sec	Platelets: (120x109/L) T Prothrombin Control: 13 sec Patient: 16 sec T P Thromboplast. Control: 30 sec Patient: 33 sec	Platelets: (2x109/L) T Prothrombin Control: 13 sec Patient: 15 sec T P Thromboplast Control: 30 sec Patient: 27 sec	Platelets: (2x109/L) T Prothrombin Control: 13 sec Patient: 22 sec T P Thromboplastin Control: 38 sec Patient: 38 sec
AgSVHB AcVHC				Negative
Renal profile				Creatinine: 33 mmol/L
Ferritin				1 000 mcg/L
Serum iron				3,77 mcg/dl
Days	4		10	
Laminate Peripheral	Leukocytes: 8x109 /L Segmented 0,40; lymphocytes 0,23; monocytes 007; myelocytes 0,01; juveniles 0,05. Toxic granulations, cytoplasmic vacuoles, left deviation. Anisomacrositosis, normochromia, spherocytes, dianocytes.		Absolute neutrophil count: 1,2 x 109/L	

Legend: GPT: glutamic-pyruvic transaminase; GOT: glutamic-oxaloacetic transaminase; AF: alkaline phosphatase; BI: indirect bilirubin; BD: direct bilirubin; GGT: ganmaglutamyl transpeptidase; LDH: lactate dehydrogenase.

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Table 2. Main results of microbiological and radiological studies.

Studies	Results according to postnatal age			
	Al nacer	**4 days**	**10 days**	**15 days**
Blood culture	No growth	No growth	No growth	No growth
Culture of epicutaneous catheter tip			No growth	
Culture of endotracheal secretions			No growth	No growth
Urine culture			No growth	
Bacteriological study of CSF			No growth	
Virological studies				Negative
Rx de Abdomen simple		Simple abdominal X-ray-Hepatomegaly, dilated bowel loops without hydro-aerial levels.		Hepatomegaly, dilated bowel loops without hydro-aerial levels.

The diagnosis of hemophagocytic syndrome was confirmed by the presence of exanthema, fever, pancytopenia, marked hepatomegaly, elevated ferritin and medullary hemophagocytosis. Specific treatment was started with dexamethasone and immunoglobulin at immunosuppressive doses. The patient died at 27 days of life with multiple organ failure.

DISCUSSION

The term hemophagocytosis refers to the characteristic finding of activated macrophages incorporating erythrocytes, leukocytes, platelets or their precursors and as a consequence, the destruction of blood cells in bone marrow and other tissues. When it occurs in the context of a highly stimulated but ineffective immune response, it is called hemophagocytic syndrome.[7]

Primary HFS is associated with specific genetic alterations, usually hereditary, in which hemophagocytosis is the only manifestation and is associated with a central defect in the formation of perforins and syntaxins or with others such as partial albinism and some types of immaturity, and may present in the first months of life.[8]

This hereditary or familial form follows an autosomal recessive pattern of inheritance and its genetic defects alter the mechanisms responsible for apoptosis (mediated by cytotoxic cells). Mutations have been described in 12 different X-linked genes.[2,4,9]

Secondary hemophagocytic syndrome can be associated with infections, neoplasms (mainly lymphoproliferative disorders), autoimmune diseases (macrophage activation syndrome) and some metabolic diseases.[9,10,11]

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Epstein Barr virus is the most frequently related infection, however, it can also be triggered by other viruses, bacteria, spirochetes, fungi and parasites.[6,10,12]

For its diagnosis the criteria proposed by the Study Group of the Histiocyte Society are used.[4] These criteria are:

1. Fever
2. Splenomegaly
3. Cytopenia (minimum involvement of two cell lines). Hemoglobin less than 90 g/L platelet count less than 100 x 109/L, total neutrophil count less than 1 x 109/L.
4. Hyperferritinemia (greater than 500 mcg/L).
5. Hypofibroginemia (less than 1.5 g/L or hypertriglyceridemia (greater than 265 mg/dl)
6. CD25 soluble (greater than 2 400 IU/ml)
7. Decreased NK cell activity (reference according to the laboratory)
8. Hemophagocytosis in bone marrow, lymph nodes or spleen.

According to these clinical and analytical criteria, the diagnosis can be established when five or more of these eight criteria are met, or when the molecular diagnosis is confirmed. Immunological and genetic studies are important, especially to diagnose familial or primary forms.[1,4,8]

Not all diagnostic criteria are present at disease onset or at neonatal presentation. The presence of hemophagocytosis is not essential for diagnosis. It is the progression in the appearance of the criteria that should alert the physician to the possible presence of HFS. The unfavorable or unusual course of symptoms of a common disease should indicate suspicion of this entity.

The reported case presented with rash, fever, pancytopenia, marked hepatomegaly and elevated ferritin of 1,000 mcg/L, accompanied by the presence of hemophagocytosis in bone marrow.

In the absence of family history or confirmatory genetic testing, it may be difficult to differentiate between the two forms of presentation (primary or secondary) as was the case in this newborn in whom genetic testing was impossible. On the other hand, neonates have a high probability of suffering bacteremia due to the immaturity of their immune system, since they are born with limited production and functional capacity of all cellular components. Coupled with this, they are exposed to multiple potentially pathogenic microorganisms in places such as the birth canal and the Neonatal Intensive Care Unit, which increases the risk of bacteremia along with the use of invasive methods such as intravascular devices. In fact, infections are among the three leading causes of death at this stage of life.

Although in this patient the microbiological results did not confirm the existence of an infection, we must remember that the main disadvantage of blood cultures as a microbiological technique is its low sensitivity in the neonatal stage, in which up to 60% of newborns with clinical sepsis have negative blood cultures,[13] so that infection cannot be ruled out as a trigger for SHF with progressive multiorgan failure that did not respond to the usual antimicrobial treatment.

The evolution of the syndrome in general is extremely unfavorable, especially during the neonatal stage, with a rapid, aggressive course and high mortality.[5]

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CONCLUSIONS

HFS is a rare disease in the neonatal stage. In most cases it is not suspected early and goes unnoticed, with very unfavorable prognostic implications for the patient. It is essential to consider it as a differential diagnosis in a severe, potentially septic newborn.

Conflict of Interest
The authors declare that there is no conflict of interest.

Authorship Contribution
YSC: conceptualization, literature review, research, formal analysis, drafting, revising and editing the manuscript.
CVS: supervision, conceptualization, design of the paper, and critical revision of the manuscript.
YMG: literature review and drafting of the manuscript.

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